REMARKS/ARGUMENTS

Applicants respectfully request reconsideration of the instant claims.

By the amendments, Applicants do not acquiesce to the propriety of any of the Office's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

In the Claims

Claims 1-7, 16-24, 26-32 and 41-43 are pending in this application. Claims 1-7, 16-24, and 26 have been withdrawn as the result of an earlier restriction requirement and are canceled herein. Claims 8-15, 25 and 33-40 were previously canceled. Applicants retain the right to present the canceled or withdrawn claims in one or more related applications.

Claim 27 has been amended to recite that the prime-boost vaccine strategy is for protection against infection by a pathogen of the genus *Mycobacterium* (support found in paragraph [0247] of the specification); wherein the second boosting immunogenic composition comprises at least one purified Mycobacteria major extracellular protein selected from the group consisting of *Mycobacterium tuberculosis* (Mtb) 23.5 kDa protein, Mtb 30 kDa protein, *Mycobacterium bovis* (MB) 30 kDa protein, MB 32A kDa protein, *Mycobacterium leprae* (ML) 23.5 kDa protein, ML 30 kDa protein, and ML 32A kDa protein (support found in originally filed claim 31); and that a protective immune response against the pathogen of the genus *Mycobacterium* is produced in the vaccinee (amendment solely for clarification).

Claim 28 has been amended to provide a definition of the abbreviation "rBCG."

Claim 29 has been amended to recite that the pathogen of the genus Mycobacterium is selected from the group consisting of *Mycobacterium tuberculosis* (Mtb), *Mycobacterium bovis* (MB), and *Mycobacterium leprae* (ML). Support for the amendments to claim 29 can be found in paragraph [0010] of the specification.

Claim 31 has been canceled.

Claim 32 has been amended to recite that the rBCG over expresses at least one Mycobacteria major extracellular protein. Support for this amendment can be found in paragraph [0066] of the instant specification.

Claim 41 has been amended to correct typographical errors.

Claim 42 has been amended to recite that the prime-boost vaccine strategy is for protection against infection by a pathogen of the genus *Mycobacterium* (support found in paragraph [0247] of the specification); and that a protective immune response against said pathogen of the genus *Mycobacterium* is produced in the vaccinee (amendment solely for clarification). A typographical error in the spelling of vaccinee was also corrected.

New claims 44-46 have been added. Support for new claim 44 can be found in originally filed claim 28. Support for new claim 45 can be found in paragraph [0010] of the specification. New claim 46 finds support in originally filed claim 27 and in the specification in paragraph [0066].

No new matter has been introduced as a result of the claim amendments.

Inventorship

Applicants hereby cancel claims 1-7, 16-24, and 26. As a result of this amendment, Marcus A. Horwitz and Günter Harth are the sole inventors of the subject matter of pending claims 27-32 and 41-46.

Therefore, Applicants hereby request that inventorship be amended under 37 C.F.R. §1.48(b) and that Michael V. Tullius be removed as an inventor on the instant application. The invention of Michael V. Tullius is no longer being claimed in the instant application.

Applicants enclose the fee under 37 C.F.R. 1.17(i) required for amending inventorship under 37 C.F.R. §1.48(b), and request that a Corrected Filing Receipt be issued.

35 U.S.C. §102 Rejections

I. Claims 27-32 and 41-43 have been rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Horwitz *et al.* (US 6,471,967, hereinafter "Horwitz"). Office Action mailed August 11, 2008 ("OA"), page 2. Applicants respectfully disagree.

The Office stated that the rejection of claims 27-32 and 41-43 can be overcome by a showing under 37 C.F.R. §1.132 that any invention disclosed but not claimed in Horwitz was derived from the inventors of the instant application and is thus not the invention by another. OA, page 2. Applicants submit herewith a declaration under 37 C.F.R. §1.132 by inventors Marcus A. Horwitz, Günter Harth and Michael V. Tullius attesting that Marcus A. Horwitz and Günter Harth are the inventors of the prime-boost strategy, the subject matter of the pending claims and that they invented the disclosed, but not claimed, subject matter in column 15 of Horwitz.

Furthermore, the inventorship of the instant application has been amended as a result of the cancellation of the withdrawn claims. The inventors of the pending claims 27-32 and 42-46 are Marcus A. Horwitz and Günter Harth.

Therefore, in light of the foregoing, Applicants respectfully request the withdrawal of the rejection of claims 27-32 and 41-43 under 35 U.S.C. §102(e) based on Horwitz.

II. Claims 27-31 and 41-43 have been rejected under 35 USC §102(e) as being allegedly anticipated by Orme *et al.* (US 7,288,261). OA, page 3. Applicants respectfully disagree.

A claim is anticipated under 35 U.S.C. §102 only if each and every element as set forth in a claim is found, either expressly or inherently described, in a single prior art reference (MPEP §2131; *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d, 628, 631, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987)). A claimed invention is anticipated only when it is "known to the art in the detail of the claim." *Karsten Manufacturing Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). In other words, not only must the limitations of the claim be shown in a single prior art reference, the limitations must be "arranged as in the claim." *Id.*

The instant claims are directed to a prime-boost vaccine strategy comprising a first priming immunogenic composition comprising a BCG and a second boosting immunogenic composition comprising at least one purified Mycobacteria major extracellular protein.

The Office stated that Orme "disclose of vaccine compositions for boosting immunity to mycobacteria when administered in mide [*sic*] life in a subject who has been vaccinated with BCG. Orme *et al.* further disclose that a preferred protein for boosting is Ag85A, a secreted Mycobacteria major extracellular protein having a molecular weight of 30 kDa." OA, pages 3-4. Applicants respectfully point out that Orme does not disclose that the Ag85A is a 30 kDa protein. Ag85A is a 32 kDa protein. See Table 1.

Solely to expedite prosecution, and not to acquiesce to the propriety of the rejection, Applicants have amended independent claim 27 to recite that the second boosting immunogenic composition comprises at least one purified Mycobacteria major extracellular protein selected from the group consisting of *Mycobacterium tuberculosis* (Mtb) 23.5 kDa protein, Mtb 30 kDa protein, *Mycobacterium bovis* (MB) 30 kDa protein, MB 32A kDa protein, *Mycobacterium leprae* (ML) 23.5 kDa protein, ML 30 kDa protein, and ML 32A kDa protein. Both independent claims 27 and 42 have been amended to clarify that the claimed prime-boost vaccine strategy produces a protective immune response against a pathogen of the genus *Mycobacterium* in the vaccinee.

While Orme discloses vaccine compositions for boosting immunity to mycobacteria, only one "boost" composition has been enabled as producing a protective immune response, the Ag85A, which corresponds to the 32A kDa protein of the instant disclosure (see paragraph [0176]). No other boost composition was demonstrated to increase the protection seen with BCG alone to induce a protective immune response.

A prior art publication must contain within its four corners a sufficient description to enable such a person to make the invention without an unreasonable amount of experimentation. *Advanced Display Systems Inc. v. Kent State University*, 212 F.3d 1272, 1282, 54 U.S.P.Q.2d 1673, 1679 (Fed. Cir. 2000), *cert. denied*, 532 U.S. 904

(2001). Furthermore, in *Dewey & Almy Chem. Co. v. Mimex Co.,* Judge Learned Hand emphasized the point that:

> No doctrine of the patent law is better established than that a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated. If the earlier disclosure offers no more than a starting point for further experiments, if its teaching will sometimes succeed and sometimes fair if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge and it is not an anticipation."

124 F.2d 986, 990, 52 U.S.P.Q. 138 (2d Cir. 1942).

Persons of ordinary skill in the art are well aware that generation of a protective immune response is not a predictable art. Orme states in column 7, lines 13-59 the unpredictability of vaccines against *Mycobacterium tuberculosis* "[i]n fact it is not known if most vaccine strategies will actually work if given to people who have an existing state of immunity, measured in any of a number of ways, to Mtb." Furthermore, Orme presents further results indicating that not all vaccine compositions were effective. For example, Figure 8 of Orme depicts an experiment wherein a boost comprising culture filtrate protein (wherein only 10% of the protein mixture consisted of the Ag85 complex) was no more effective than saline in boosting immunity to *M. tuberculosis* after a prior immunization with BCG. Additionally, Orme only discloses boosting with the Ag85A protein in the presence of an immunostimulatory molecule, IL-2 (column 6, lines 25-36) and does not provide any controls for IL-2 alone as a boosting composition. Therefore it is impossible for a person of ordinary skill in the art to determine if the efficacy of Orme's boost composition is due to the Ag85A protein or to the immunostimulatory IL-2. It is well known that boosting with certain immunostimulatory molecules can induce protective immunity in individuals who had previously been immunized against certain pathogens.

Therefore, Orme does not provide an enabling disclosure for all proteins of *M. tuberculosis*, much less the claimed proteins of *M. tuberculosis*, *M. bovis* and *M. leprae* (Mtb 23.5 kDa protein, Mtb 30 kDa protein, MB 30 kDa protein, MB 32A kDa protein, ML

23.5 kDa protein, ML 30 kDa protein, and ML 32A kDa protein). Orme only provides an enabling disclosure for the Ag85A protein in the presence of a strong immunostimulatory molecule, IL-2. As a result, Orme does not anticipate the subject matter of the pending claims. Therefore, in light of the foregoing, Applicants respectfully assert that claims 27-32 and 41-46 are novel over the cited prior art and respectfully request the reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. §102 based on Orme.

35 U.S.C. §103 Rejections

Claims 27-32 and 41-43 have been rejected under 35 USC §103(a) as allegedly being unpatentable over Horwitz *et al.* (PNAS 97:13853-13858, 2000, hereinafter "Horwitz 2") in view of Orme. OA, page 4. Applicants respectfully disagree.

To maintain a proper rejection under 35 U.S.C. §103, the Office must meet four conditions to establish a *prima facie* case of obviousness. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by

demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966).

Presently, the Office has not established a *prima facie* obviousness case under 35 U.S.C. §103 for at least the following reasons: (1) the combination of references does not teach all of the elements of the pending claims and (2) the "obvious to try" standard cannot support the rejections. Each of these reasons is addressed in turn.

I. The Cited References do not Teach all of the Elements of the Pending Claims

A. The Instant Claims

The instant claims are directed to a prime-boost vaccine strategy for protection against infection by a pathogen of the genus *Mycobacterium*; comprising administering a first priming immunogenic composition to a vaccinee wherein said first priming immunogenic composition is a BCG (claims 27-32, 41-45) or identifying an individual who had previously been immunized with BCG (new claim 46); administering a second boosting immunogenic composition comprising at least one purified Mycobacteria major extracellular protein consisting of *M. tuberculosis* 30 kDa protein (claims 42-45) or selected from the group consisting of *Mycobacterium tuberculosis* (Mtb) 23.5 kDa protein, Mtb 30 kDa protein, *Mycobacterium bovis* (MB) 30 kDa protein, MB 32A kDa protein, *Mycobacterium leprae* (ML) 23.5 kDa protein, ML 30 kDa protein, and ML 32A kDa protein (claims 27-32, 41 and 46); wherein a protective immune response against the pathogen of the genus *Mycobacterium* is produced in the vaccinee

B. The Cited Art

1. Horwitz 2

According to the Office, Horwitz 2 discloses recombinant BCG expressing the *M. tuberculosis* 30 kDa major secretory protein. OA, page 5. The Office acknowledges that Horwitz does "not teach of administering a second boosting immunogenic composition which is a purified Mycobacteria major extracellular protein." OA, page 5.

2. Orme

The Office asserts that Orme "teach of vaccine compositions for boosting immunity to mycobacteria specifically for individuals who were previously vaccinated with BCG. OA, page 5. As discussed above, Orme teaches and suggests boosting immunity to mycobacteria in individuals previously vaccinated by BCG with *M. tuberculosis* proteins. Orme only enables production of a protective immune response by boosting with the Mtb Ag85A protein.

Therefore the combination of Horwitz and Orme does not teach or suggest the claimed prime-boost strategy wherein the boost comprises at least one purified Mycobacteria major extracellular protein selected from the group consisting of Mtb 23.5 kDa protein, Mtb 30 kDa protein, MB 30 kDa protein, MB 32A kDa protein, ML 23.5 kDa protein, ML 30 kDa protein, and ML 32A kDa protein.

II. It is not "Obvious to Try" the Claimed Invention in Light of the Prior Art References

In order to rely on the "obvious to try" standard under 35 U.S.C. §103, the Office must establish that there were a finite number of identified, predictable solutions with a reasonable expectation of success. *In re Fine*, 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988); *KSR Int'l Co. v. Teleflex.,* 127 S.Ct. 1727; *see also* Examination Guidelines, 72 Fed. Reg. at 57,529. Importantly, the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988).

As Orme himself demonstrates, not all combinations of vaccines produce protection against challenge with infectious pathogen (see Figure 8). Therefore, the behaviors of the different boosting compositions are not predictable and the obvious to try standard cannot be applied.

For all of the reasons described above, the Office has not established a *prima facie* case of obviousness of pending claims 27-32 and 41-43 over Horwitz *2* in view of Orme. The cited prior art references, in combination, do not disclose all the claim

limitations, and it is not "obvious to try" the claimed invention in light of the prior art references. The Office is respectfully requested to reconsider and withdraw the rejection of claims 27-32 and 41-43 under 35 USC §103 based on Horwitz 2 in view of Orme.

CONCLUSION

Based on the foregoing, Applicants respectfully assert that pending claims 27-32 and 41-46 are in condition for allowance and request a timely Notice of Allowance be issued in this application.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

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